SUPPLEMENTARY INFORMATION

Prevalence of Single and Multiple Natural NS3, NS5A and NS5B Resistance-Associated Substitutions in Hepatitis C Virus Genotypes 1-4 in Italy

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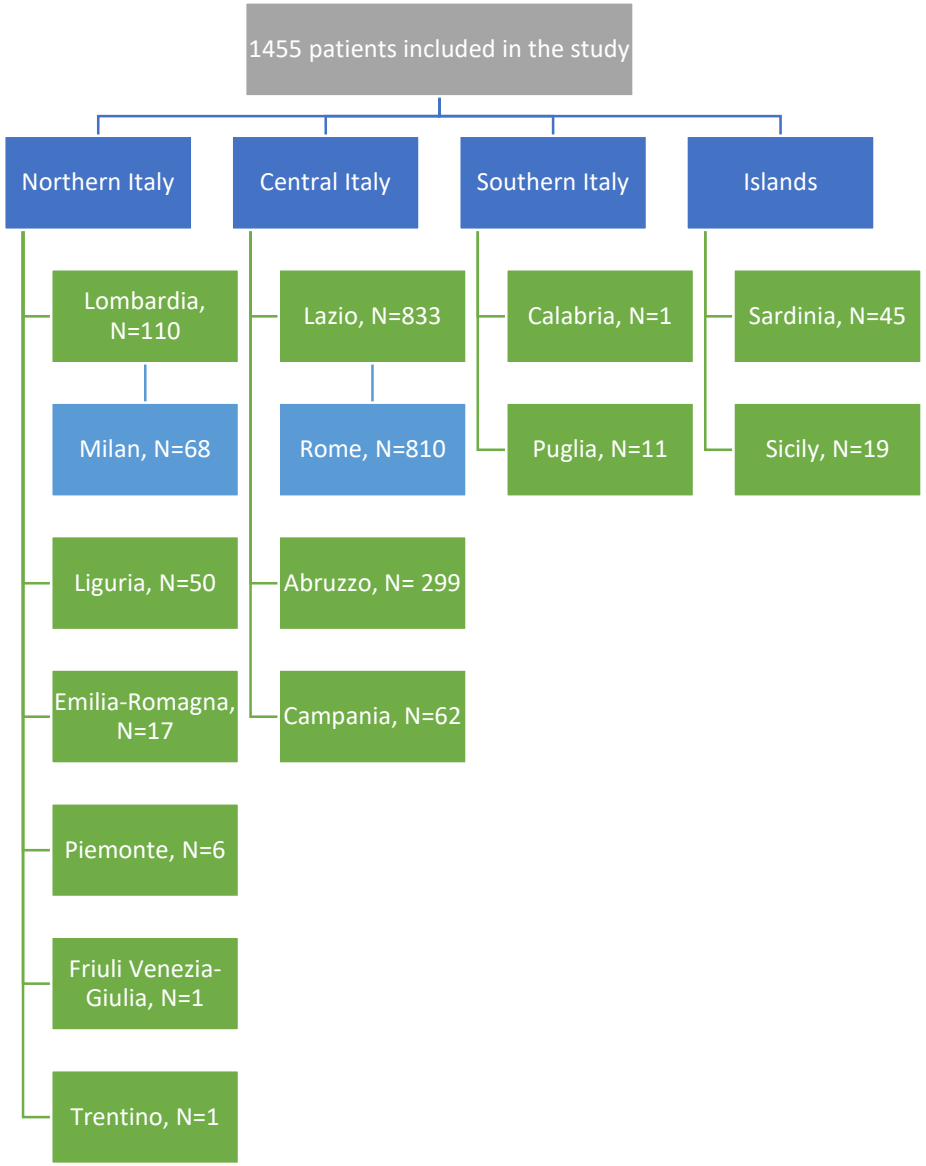
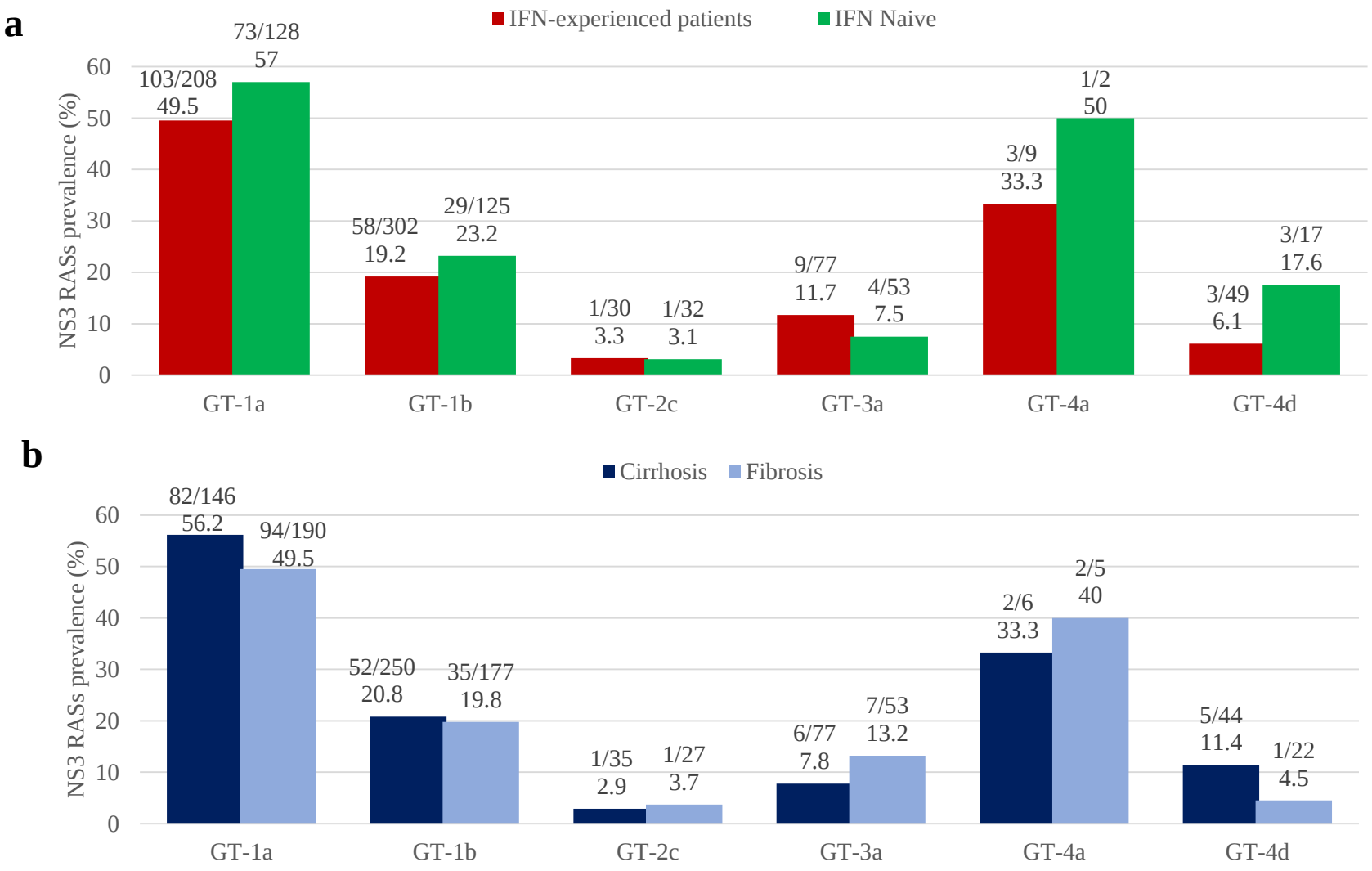
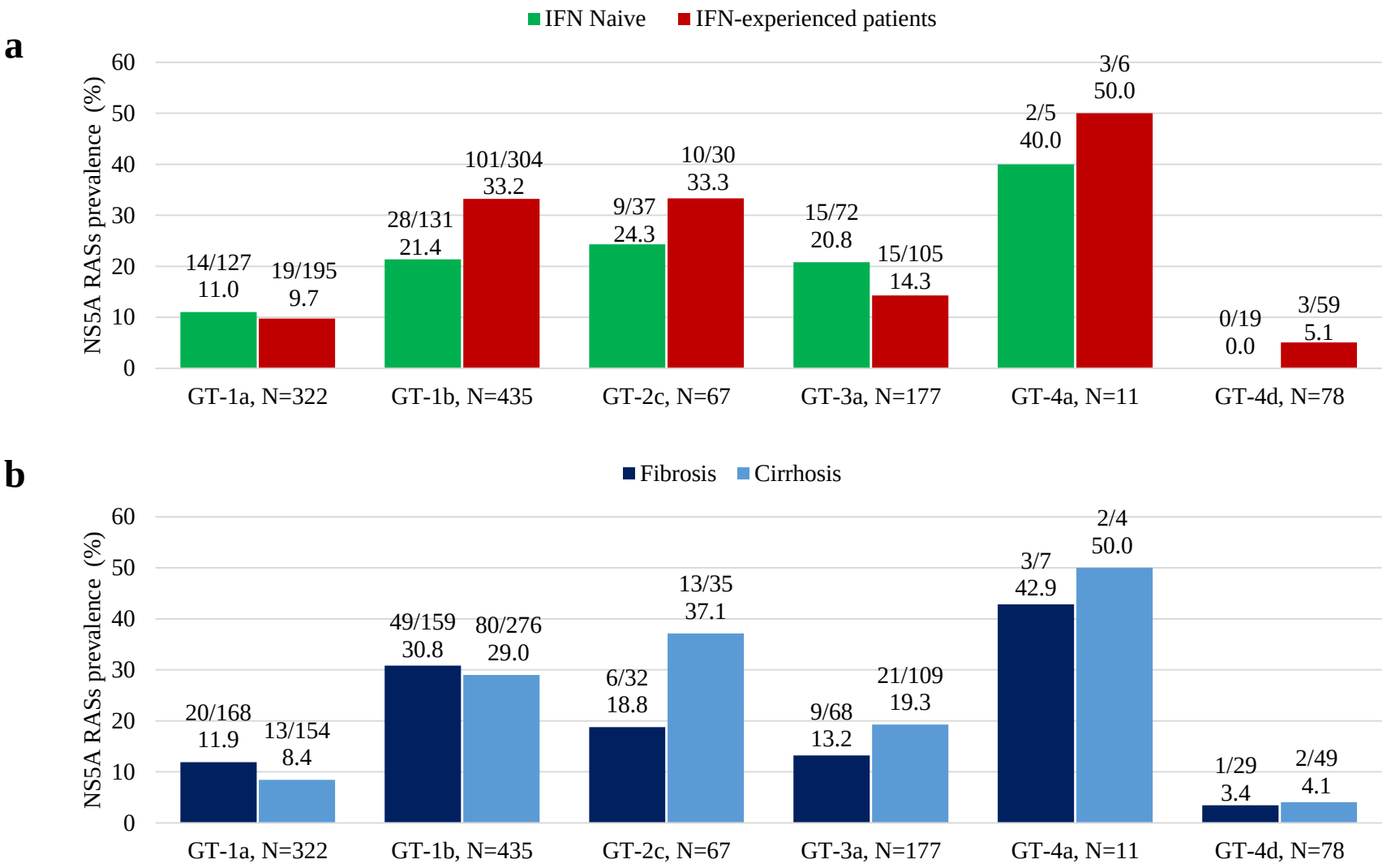


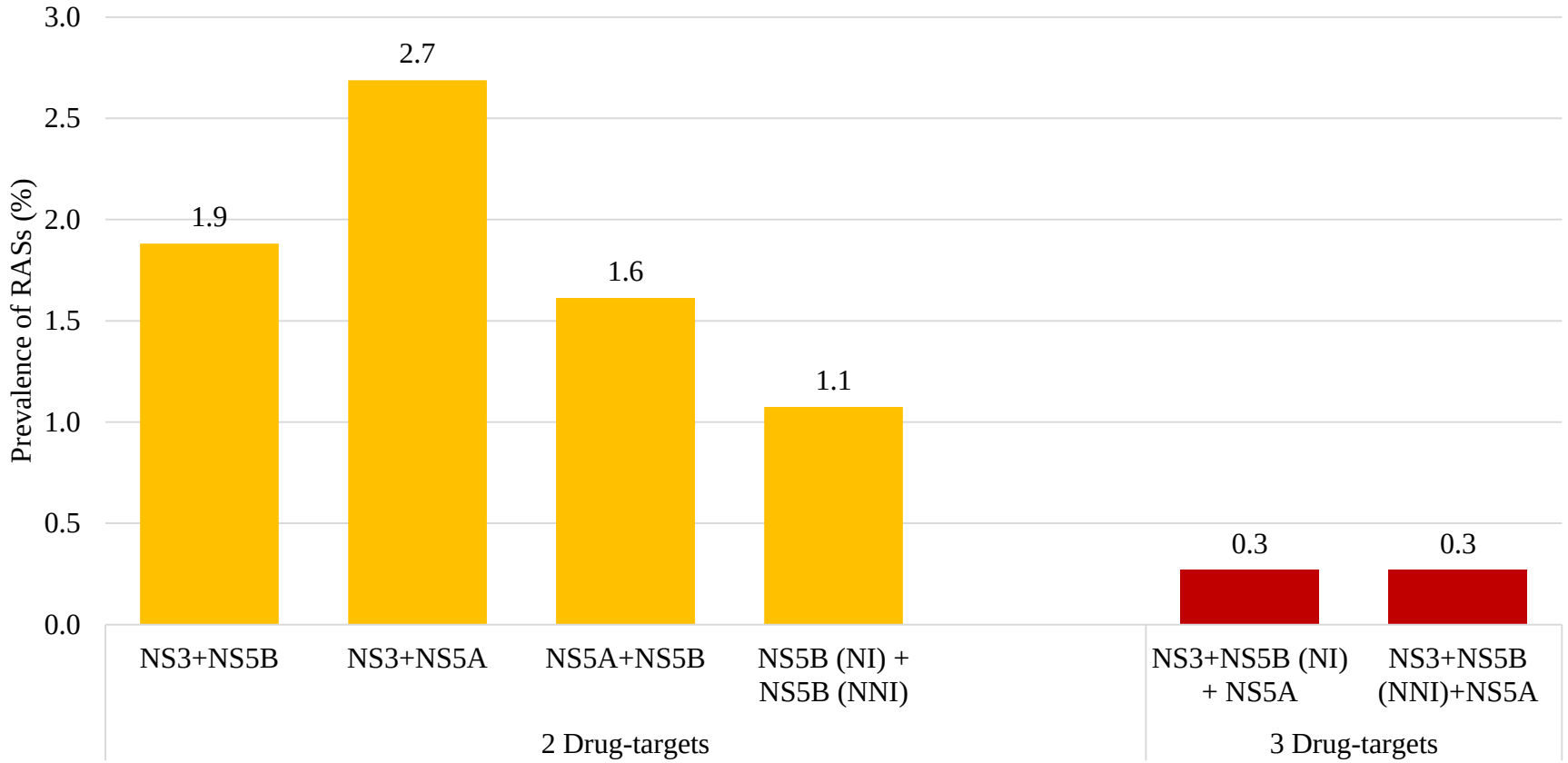
Supplementary Figure S1. Patients' enrollment among Italian regions. The number of patients enrolled in each Italian region is reported, along with focus on main cities as Milan and Rome.



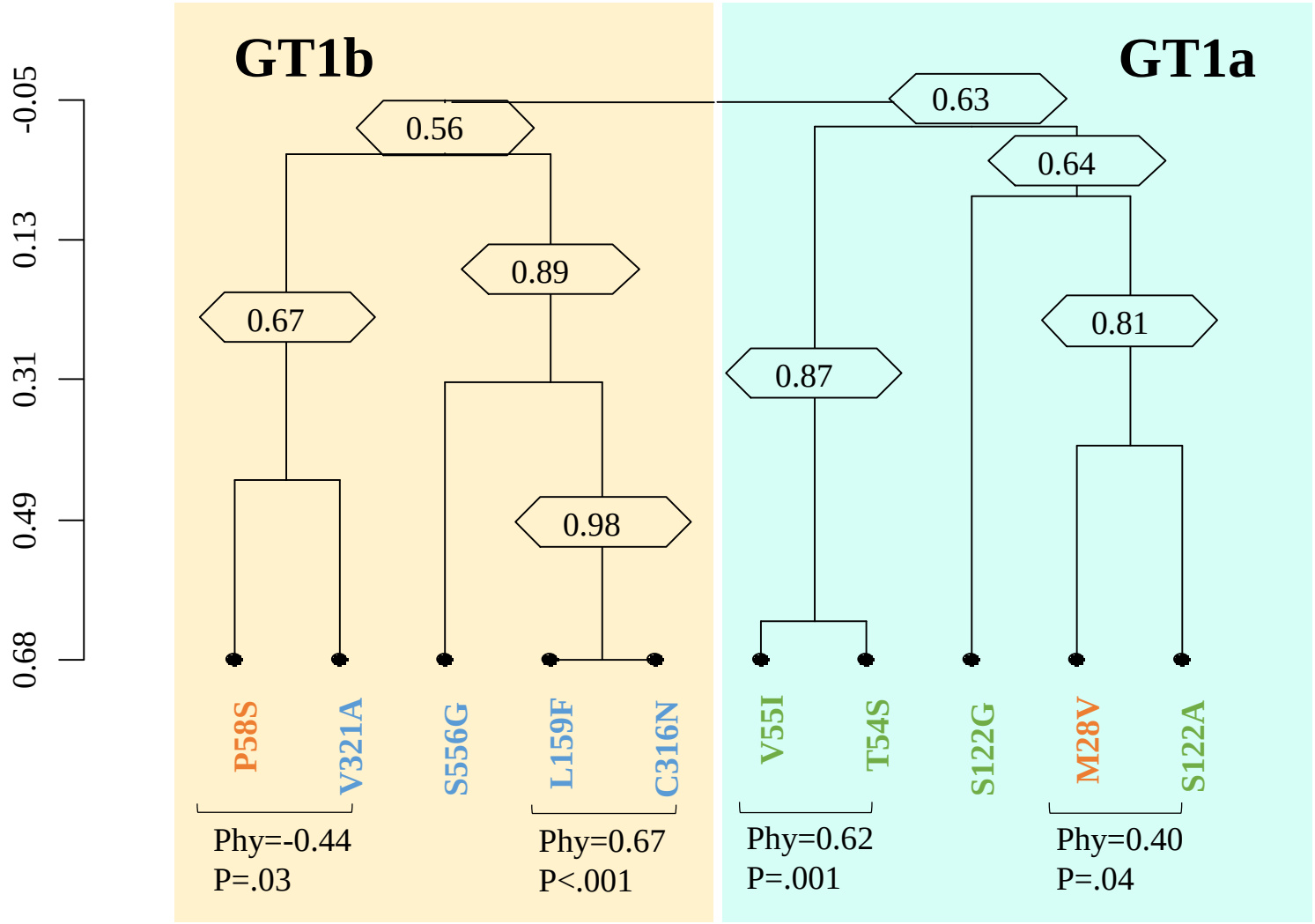
Supplementary Figure S2. Prevalence of natural NS3 RASs according to patients' characteristics and viral genotypes. NS3 RASs prevalence according to previous interferon treatment experience (**a**) or presence of cirrhosis (**b**) are reported. IFN, interferon; RASs, resistance associated substitutions.



Supplementary Figure S3. Prevalence of natural NS5A RASs according to patients' characteristics and viral genotypes. NS5A RASs prevalence according to previous interferon treatment experience (**a**) or presence of cirrhosis (**b**) are reported. IFN, interferon; RASs, resistance associated substitutions.



Supplementary Figure S4. Prevalence of multiclass resistance. Multiple RASs on 2 drug-classes are reported in yellow; multiple RASs on 3 drug-targets are in red. NS5B-NI, nucleoside NS5B polymerase inhibitors; NS5B-NNI, nonnucleoside NS5B polymerase inhibitors; RASs, resistance associated substitutions.



Supplementary Figure S5. Covariation analysis of natural NS3, NS5A and NS5B RASs.
NS3-RASs are reported in green, NS5A-RASs in orange, and NS5B-RASs in blue. Binomial-correlation coefficient (phi) was calculated to assess covariation among RASs, either on the same or on different genomic regions. Statistically significant pairs of RASs were identified by Fisher's exact test, and then corrected for multiple-testing by Benjamini–Hochberg method (FDR =.05). In order to identify and summarize higher-order interactions of RASs, we transformed the pairwise phi correlation coefficients into dissimilarity values. A dendrogram was then computed by hierarchical clustering, and its stability was assessed from 100 bootstrap replicates. All analyses were performed in R software. GT, genotype; RASs, resistance associated substitutions.